FAO SPECIFICATIONS AND EVALUATIONS

FOR PLANT PROTECTION PRODUCTS

GLYPHOSATE

N-(phosphonomethyl)glycine

2000/2001

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

TABLE OF CONTENTS

GLYPHOSATE

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INTRODUCTION

FAO establishes and publishes specifications* for technical material and related formulations of plant protection products with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

Since 1999 the development of FAO specifications follows the **New Procedure**, described in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products"(FAO Plant Production and Protection Page No. 149). This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the "FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent."
FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

Part One: The Specification of the technical material and the related formulations of the plant protection product in accordance with chapter 4, 5 and 6 of the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products".

Part Two: The Evaluation Report(s) of the plant protection product reflecting the evaluation of the data package carried out by FAO and the Panel of Experts. The data are to be provided by the manufacturer(s) according to the requirements of Appendix A, annex 1 or 2 of the "Manual on the development and use of FAO specifications for plant protection products" and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO Specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other methods of synthesis. FAO has the possibility to extend the scope of the specifications to similar products, but only when the Panel of Experts has been satisfied that the additional products are equivalent to those which formed the basis of the reference specification.

* Footnote: The publications are available on Internet at
http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/

PART ONE

SPECIFICATIONS

GLYPHOSATE

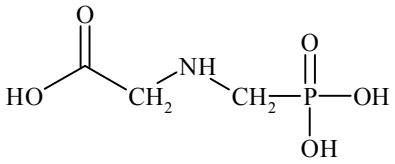
FAO SPECIFICATIONS AND EVALUATIONS FOR
PLANT PROTECTION PRODUCTS

GLYPHOSATE

INFORMATION

COMMON NAME : Glyphosate (ISO)

Structural formula



EMPIRICAL FORMULA: $C_3H_8NO_5P$

RMM: 169

CAS REGISTRY NUMBER: 1071-83-6

CIPAC CODE NUMBER: 284

CHEMICAL NAMES: *N*-(phosphonomethyl)glycine (IUPAC and CA)

GLYPHOSATE ACID TECHNICAL
284/TC (2000/2001)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (284/2000 + 2001). It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation reports (284/2000 + 2001) as PART TWO forms an integral part of this publication.

.1 DESCRIPTION

The material shall consist of glyphosate (acid), together with related manufacturing impurities. It shall be a white dry powder, free from visible extraneous matter and added modifying agents.

.2 ACTIVE INGREDIENT

.2.1 Identity tests (284/TC/(M)/2, CIPAC 1C, p.2132),

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

.2.2 Glyphosate acid (284/TC/(M)/3, CIPAC 1C, p.2132) (AOAC 983.10, 1990)

The glyphosate acid content shall be declared (not less than 950 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

.3 RELEVANT IMPURITIES

.3.1 Formaldehyde (Note 1)

Maximum 1.3 g/kg of the glyphosate acid content found under .2.2.

.3.2 *N*-Nitrosoglyphosate (Note 2)

Maximum 1 mg/kg

.3.3 Insolubles in 1 M NaOH (MT 71)

Maximum: 0.2 g/kg

Note 1 The analytical method for determination of Formaldehyde is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

Note 2 The analytical method for determination of N-Nitrosoglyphosate is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

GLYPHOSATE ACID TECHNICAL CONCENTRATES
284/TK (2000/2001)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (284/2000 + 2001). It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation reports (284/2000 + 2001) as PART TWO forms an integral part of this publication.

.1 DESCRIPTION

The material shall consist of glyphosate (acid) together with related manufacturing impurities. It shall be a white to greyish wet cake, free from visible extraneous matter and added modifying agents.

.2 ACTIVE INGREDIENT

2.1 Identity tests (284/TC/(M)/2, CIPAC 1C, p.2132),

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

.2.2 Glyphosate acid (284/TC/(M)/3, CIPAC 1C, p.2132) (AOAC 983.10, 1990)

The glyphosate acid content shall be declared (not less than 950 g/kg on a dry basis) and, when determined, the mean measured content obtained shall not differ from that declared by more than ± 20 g/kg.

.3 IMPURITIES

.3.1 Formaldehyde (Note 1)

Maximum 1.3 g/kg of the glyphosate acid content found under .2.2.

.3.2 *N*-Nitrosoglyphosate (Note 2)

Maximum 1 mg/kg

.3.3 Loss on drying (MT 17.3, Sample weight: 10 g; temperature: 105°C, time: 3 hours.).

The loss on drying shall be declared and, when measured the average loss shall be not more than 200 g/kg.

.3.4 Insolubles in 1 M NaOH (MT 71)

Maximum: 0.2 g/kg, dry weight basis

Note 1 The analytical method for determination of Formaldehyde is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

Note 2 The analytical method for determination of N-Nitrosoglyphosate is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

GLYPHOSATE ISOPROPYLAMINE SALT TECHNICAL CONCENTRATES 284 /TK (2000)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (284/2000). It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report (284/2000) as PART TWO forms an integral part of this publication.

.1 DESCRIPTION

The material shall consist of glyphosate (acid), complying with the requirements of FAO specification 284/TC, together with related manufacturing impurities in the form of the isopropylamine salt, and shall be a solution in water, free from visible extraneous matter and added modifying agents except for the diluent.

.2 ACTIVE INGREDIENT

2.1 Identity tests (284/TC/(M)/2, CIPAC 1C, p.2132)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

.2.2 Glyphosate acid (284/TC/(M)/3, CIPAC 1C, p.2132) (AOAC 983.10, 1990)

The glyphosate acid content shall be declared, (g/l or g/kg at 20 ± 2°C) and, when determined, the mean measured content shall not differ from that declared by more than the appropriate FAO proposed tolerance as given below:

Declared content in g/kg or g/l at 20±2°C	Tolerance
above 250 up to 500	5 % of the declared content
above 500	25 g/kg or g/l

.3 IMPURITIES

.3.1 Formaldehyde (Note 1)

Maximum 1.3 g/kg of the glyphosate acid content found under .2.2.

.3.2 *N*-Nitrosoglyphosate (Note 2)

Maximum: 1 mg/kg

.3.3 Insolubles in Water (MT 10.2)

Maximum: 0.1 g/kg, dry weight basis

.4 PHYSICAL PROPERTIES

.4.1 pH range (MT 75) (Note 3)

pH 4.5 to pH 6.8

Note 1 The analytical method for determination of Formaldehyde is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

Note 2 The analytical method for determination of N-Nitrosoglyphosate is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

GLYPHOSATE SOLUBLE CONCENTRATES
284/SL (2000)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (284/2000). It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report (284/2000) as PART TWO forms an integral part of this publication.

.1 DESCRIPTION

The material shall consist of a solution of technical glyphosate, complying with the requirements of FAO specification 284/TC in the form of a soluble salt, dissolved in water, together with any necessary formulants.
It shall be in the form of a clear or opalescent liquid, free from suspended matter and sediment, to be applied as a true solution of the glyphosate salt in water.

.2 ACTIVE INGREDIENT

2.1 Identity tests (284/TC/(M)/2, CIPAC 1C, p.2132)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

.2.2 Glyphosate (284/SL/(M)/3, CIPAC 1C, p.2134) (AOAC 983.10, 1990)

The glyphosate acid content shall be declared for each specific soluble concentrate (g/kg or g/l at 20 2 ^{o}C, Note 2) and, when determined, the content measured shall not differ from that declared by more than the following amounts:

Declared content in g/kg or g/l	Tolerance
up to 25	15 % of the declared content
25 to 100	10 % of the declared content
100 to 250	6 % of the declared content
250 to 500	5 % of the declared content
above 500	25 g/kg or g/l
in each range the upper limit is included	

.3 IMPURITIES

.3.1 Formaldehyde (Note 2)

Maximum 1.3 g/kg of the glyphosate acid content found under .2.2.

.3.2 *N*-Nitrosoglyphosate (Note 3)

Maximum 1 mg/kg

.4 **PHYSICAL PROPERTIES** (Note 4)

.4.1 Solution stability (MT 41)

After the stability test at 54°C (.5.2), the product, after dilution with CIPAC Standard Water D and standing for 18 h. at 30 2°C (Note 5), shall give a clear or opalescent solution, free from more than a trace of sediment or, particles produced shall pass through a 45 µm test sieve.

.4.2 Persistent foam (MT 47.2)

Maximum 60 ml after 1 minute.

.5 **STORAGE STABILITY**

.5.1 Stability at 0°C (MT 39.3)

After storage at 0 ± 2°C for 7 days, the volume of solid and/or liquid which separates shall be not more than 0.3 ml.

.5.2 Stability at elevated temperature (MT 46.3)

After storage at 54 ± 2°C for 14 days, the average determined glyphosate content must not be lower than 95 % relative to the determined content found before storage and the product shall continue to comply with .3.3.1, 3.3.2 and .4.1.

Note 1 Where the buyer requires both g/kg and g/l at 20oC then, in case of dispute, the analytical results shall be calculated as g/kg.

Note 2 The analytical method for determination of Formaldehyde is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

Note 3 The analytical method for determination of N-Nitrosoglyphosate is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

Note 4 In the case of isopropylamine salt containing formulations and depending on the climatical conditions the pH of the formulation has to be taken into account

because the equilibrium glyphosate acid-glyphosate monoispropylamine salt-diisopropylamine salt and properties of the formulants added will determine the stability towards crystallisation of glyphosate acid

Note 5 Unless another temperature is specified.

GLYPHOSATE WATER SOLUBLE GRANULES
284/SG (2000)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (284/2000). It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report (284/2000) as PART TWO forms an integral part of this publication.

.1 DESCRIPTION

The material shall consist of granules containing technical glyphosate, complying with the requirements of FAO specification 284/TC, in the form a suitable salt, together with suitable carriers and formulants.
It shall be homogeneous, free from visible extraneous matter and/or hard lumps, free flowing, and essentially non-dusty. The glyphosate salt shall be soluble in water (Note 1). Insoluble carriers and formulants shall not interfere with compliance with .4.2.

.2 ACTIVE INGREDIENT

.2.1 Identity test (284/SG/(M)/2, CIPAC H, p.182), (Note 2)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

.2.2 Glyphosate (284/SG/(M)/3, CIPAC H, p.182)

The glyphosate acid or salt content shall be declared (g/kg) and, when determined, the content obtained shall not differ from that declared by more than the following amounts:

Declared content in g/kg	Tolerance
100 to 250	6 % of the declared content
250 to 500	5 % of the declared content
above 500	25 g/kg
in each range the upper limit is included	

.3 IMPURITIES

.3.1 Formaldehyde (Note 2)

Maximum 1.3 g/kg of the glyphosate acid content found under .2.2.

.3.2 *N*-Nitrosoglyphosate (Note 3)

Maximum 1 mg/kg

.4 PHYSICAL PROPERTIES

.4.1 Degree of dissolution and solution stability (MT 179)

Residue of formulation retained on a 75 µm test sieve after dissolution in CIPAC Water D at 30 2°C (Note 4).
Maximum: 2 % after 5 minutes.
Maximum: 0.05 % after 18 hours.

.4.2 Persistent foam (MT 47.2)

Maximum: 40 ml after 1 minute.

.4.3 Dustiness (MT 171)

Essentially non-dusty with a maximum of 15 mg (0.05 % wt) collected dust applying the gravimetric method.

.4.4 Flowability (MT 172)

98 % to pass a 5 mm test sieve after 20 drops of the sieve.

.5 STORAGE STABILITY

.5.1 Stability at elevated temperatures (MT 46.3)

After storage at 54 ± 2°C for 14 days, the average determined glyphosate content shall not be lower than 95 % relative to the determined content found before storage and the product shall continue to comply with .3.1, .3.2, .4.1, 4.3 and 4.4 as required.

Note 1 Glyphosate acid as the sodium- or ammonium salt.

Note 2 The analytical method for determination of Formaldehyde is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

Note 3 The analytical method for determination of N-Nitrosoglyphosate is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

Note 4 Unless another temperature is specified.

PART TWO

EVALUATION REPORT(S)

GLYPHOSATE

FAO SPECIFICATIONS AND EVALUATIONS FOR PLANT PROTECTION PRODUCTS

GLYPHOSATE

EVALUATION REPORT 284/2000

EXPLANATION

Glyphosate was scheduled as an existing FAO specification to be reviewed in 1999 under the procedure introduced by FAO in 1998 (FAO Panel, 1998).

The current FAO specifications for glyphosate acid technical concentrates (FAO Specification 284/TK/S, 1991) and glyphosate soluble concentrates (FAO Specification 284/SL/S , 1991) were published in 1992 (AGP:CP/301) with a correction in 1994 (AGP:CP/311).

Glyphosate was evaluated for the first time by JMPR for toxicology and residues in 1986, for residues again in 1988 and 1994, and for toxicology and residues in 1997.

The new draft specifications were submitted 1999 by Monsanto and Cheminova jointly. Data were provided by both companies.

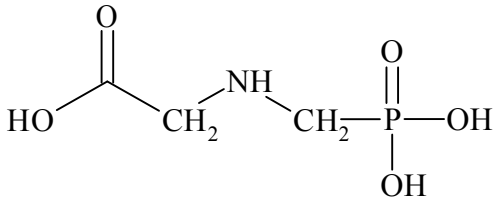
USES

Glyphosate is a non-selective contact herbicide with a broad spectrum of applications in agriculture, horticulture viticulture, forestry orchards, plantation crops, amenities, home gardening and greenhouses for the control of annual and perennial grasses and broad-leaved weeds. Furthermore it is used for weed control on aquatic areas, industrial areas, railroad tracks and on other non-cultivated areas. Besides the weed control it is used for root sucker control, for reseeding of grassland and to facilitate harvest. In addition there are uses in transgenic crops which are tolerant to glyphosate (rape, maize, soybeans, in sugar and fodder beets, cotton).

IDENTITY

ISO common name : Glyphosate
Chemical name
IUPAC: *N*-(phosphonomethyl)glycine
CA: *N*-(phosphonomethyl)glycine
CAS No: 1071-83-6
EINECS No: 213-997-4
CIPAC No: 284
Synonyms: MON 0573
CP 67573

Structural formula:



Molecular formula: $C_3H_8NO_5P$
Molecular weight: 169
Identity test: HPLC method (284/TC/(M)/3, CIPAC 1C, p.2132), retention time.
Spectrophotometric method:
Reaction of glyphosate under acidic conditions to form *N*-nitroso-glyphosate. UV determination at 243 nm.

PHYSICAL AND CHEMICAL PROPERTIES OF PURE ACTIVE INGREDIENT

Vapour pressure:	1.3 10^{-5} Pa at 25°C Method: EEC A4 Substance purity: 986 g/kg
Melting point:	189.5°C ± 0.5°C Method: OECD 102 Substance purity: 999 g/kg
Temperature of decomposition:	199°C ± 1°C Method: OECD 102 Substance purity: 999 g/kg
Solubility in water:	10.5 g/l at 20°C Method OECD 105 Substance purity: 995 g/kg
Octanol/water partition coefficient:	log K_{ow} = < -3.2 at 25°C equivalent K_{ow} = < 6 10^{-4} (same K_{ow} was found at pH 5, 7 and 9) Method OECD 107 Substance purity: 974 g/kg

Hydrolysis:	glyphosate can be considered hydrolytically stable at pH 3, 6 and 9 at 5 or 35°C (half-life >> 30 days). ^{14}C-glyphosate can be considered hydrolytically stable at pH 5, 7 and 9 at 25°C (half-life >> 30 days). Method US EPA similar to OECD 111. Substance purity: 974 g/kg
Photolysis	No change noted after 24 hours exposure to sunlight. Method: US EPA FIFRA subdivision D- no 63-13.

CHEMICAL COMPOSITION AND PROPERTIES OF THE TECHNICAL MATERIAL (TC and TK)

All necessary information on the manufacturing process and the impurity profile including batch analysis was presented by both of the data submitters in the proposal.

Methods of manufacture –

A summary of the commercially confidential manufacturing process was provided to the Meeting from both of the companies. The Meeting was also provided with information on the nature of the impurities at or exceeding 1 g/kg and their maximum limits in technical material.

Purity (content of active ingredient): glyphosate content in technical material, not less than 950 g/kg.

The impurity profile submitted by Monsanto was different from that provided to the German authorities before with regard to the maximum limits of the specified impurities, but no new impurities were specified. The impurity profile of Cheminova was in line with the information submitted to the German authorities. The impurity profiles have been compared by the German authorities and were regarded to be equivalent with regard to toxicological and ecotoxicological properties.

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on impurities present at or above 1 g/kg, from both companies. The mean mass balances of the batches were 994.5 (Monsanto) and 1045 g/kg (Cheminova).

HAZARD SUMMARY

Evaluations referred to: JPMR 1986/97
ICPS Environmental Health Criteria 159
Agriculture Canada, Discussion Document 1991

Hazard classification. normal use: WHO: Unlikely to present acute hazard in

Table 1. Acute toxicity of glyphosate acid technical material

Species	Test	Test result
Rat	Oral LD_{50}	> 5000 mg/kg
Rat	Dermal LD_{50}	> 5000 mg/kg
Rabbit	Skin irritancy	essentially non-irritating
Rabbit	Eye irritancy	moderate/severe irritation
Guinea Pig	Skin sensitization	not a dermal sensitizer

Table 2. Summary of NOAELs for studies on short term toxicity, long term toxicity and carcinogenicity (EHC 159, 1994*)

Species	Test compound	Dose levels mg kg^{-1} diet unless otherwise stated	Effects, dose level (mg/kg diet)	NOAEL [mg/kg diet] mg kg^{-1} b.w. d^{-1}
Short-term studies				
Mouse	Technical glyphosate	5000, 10000, 50000	decreased growth and increased weights in brain, heart, kidneys (50000)	[10000] 1890 m, 2730 f
Mouse	Technical glyphosate	3125, 6250, 12500, 25000, 50000	reduced weight gain (50 000), lesions of salivary glands ($\geq$ 6250)	[3125] 507
Rat	Technical glyphosate	1000, 5000, 20000	no adverse effects	[20000]** 1267**m 1623**f
Rat	Technical glyphosate	200 to 12500	no adverse effects	[12500] NG**
Rat	Technical glyphosate	3125, 6250, 12500, 25000, 50000	increased AP and ALAT ($\geq$6250), increased haematocrit and red cell parameters ($\geq$12 500), increased bile acids, decreased sperm counts ($\geq$25 000), histological alterations in salivary glands ($\geq$3 125), reduced weight gain ($\geq$25 000)	[< 3125] < 205 m < 213 f
Dogs	Technical glyphosate	20, 100, 500 mg kg^{-1} bw	no adverse effects	500**

Cattle	Roundup	400, 500, 630, 790 mg kg^{-1} bw	decreased feed intake (≥630 mg kg^{-1} bw d^{-1}), diarrhoea (≥500), increased blood parameters (790)	400
Long-term studies				
Mouse	technical glyphosate	1000, 5000, 30000	decreased growth (30 000), increased incidence of hepatocyte hypertrophy and necrosis (30 000), increased incidence of urinary bladder epithelial hyperplasia (30 000)	[5000] 814
Rat	technical glyphosate	2000, 8000, 20000	decreased growth (20 000), increased liver weights (20 000), increased incidences of degenerative lens changes (20 000) and of gastric inflammation (8000 and 20 000)	[8000] 410
Rat	technical glyphosate	60, 200, 600	slightly decreased growth (600)	a

* note taken of corrigenda on the IPCS web site; m = males; f = females;
** Highest dose tested; NG, not given;
[a] The slight effect at 600 mg/kg diet (32 mg/kg bw) is considered marginal in the light of the absence of an effect on growth at higher dose levels (2000 and 8000 mg/kg diet) in a more recent 2-year study in rats.

Table 3. Summary of teratogenicity and reproduction studies on glyphosate (EHC 159)

Species	Test compound	Dose levels	Effects, dose level	NOAEL[a] mg kg^{-1} b.w. d^{-1}
Rat	technical glyphosate	300, 1000, 3500 mg kg^{-1} diet d^{-1} gestation days 6-19	mortality, clinical signs and decreased growth in dams, early resorptions, decreased numbers of implantations and visible fetuses, decreased ossification of fetal sternebrae (all at 3500 only); no fetal malformations	1000
Rabbit	technical glyphosate	75, 175, 350 mg/kg body weight, gestation days 6-27	diarrhoea and soft stools (350, slight at 175), nasal discharge (350)	175
Rat	technical glyphosate	3, 10, 30 mg/kg body	increased incidence of renal tubular dilation in	< 30[b]

		weight given in diet, 3 generations	F_{3b} male pups (30)	
Rat	technical glyphosate	2000, 10 000, 30 000 mg/kg diet, 2 generations	soft stools of parents (30 000), decreased litter size (30 000), decreased body weights of parents and pups (30 000 and 10 000)	100[b] [2000 mg/kg diet]

[a] Based on all observed effects (both in dams and offspring)

[b] There is some discrepancy in the results, and in the NOAELs, of the two reproduction studies carried out with technical glyphosate; the renal effects in the 3-generation study were not reproduced in the more recent 2-generation study with higher dose levels.

Table 4. Genotoxicity testing, in Vitro Mutagenicity studies (Monsanto)

Test system	Target cells	Results
Bacterial mutation assay with and without metabolic activation	Salmonella typhimurium TA98, TA100, TA1535 TA 1538; *B. subtilis; E. coli*	negative
Mammalian cell gene mutation assay with and without metabolic activation	Chinese Hamster ovary	negative
Mammalian cell cytogenetic Assay	Human Lymphocytes (chromosomal aberrations)	negative
Rat hepatocyte culture unscheduled DNA synthesis assay	Rat hepatocytes UDS	negative

Table 5. In vivo Mutagenicity studies (Monsanto)

Test system	Target cells	Results
Mouse bone marrow Micronucleus assay	Mouse bone marrow	negative

Acute toxicity

Glyphosate acid and its salts exhibited a low acute toxicity in laboratory animals by the oral and dermal route with LD_{50} values greater than 5000 mg/kg bw
Regarding primary irritation, glyphosate acid and the salts were found to be non-irritant, at least to intact skin. In contrast, undiluted glyphosate acid was found to be strongly irritant to rabbit eyes. There was markedly less eye irritation observed with the salts.
Sensitization was not observed with either glyphosate acid or the salts.

Short-term toxicity

Subacute and subchronic oral toxicity studies also show a low toxicity of glyphosate. Repeated dermal exposure of rabbits and rats to glyphosate did not result in any systemic effects. Dermal irritation was not observed.

Mutagenicity / carcinogenicity

Glyphosate was examined for mutagenicity in a wide range of test systems covering all relevant endpoints in vitro as well as in vivo.
From this large database, it can be concluded that the active ingredient does not exhibit a mutagenic risk to humans. It should be also taken into consideration that there is no evidence of carcinogenic effects in humans, although glyphosate products have been in world-wide use for many years.

Reproduction toxicity

Multigeneration studies in rats did not indicate a specific hazard of glyphosate for reproduction.
Glyphosate is not teratogenic. The NOEL for developmental effects was 1000 mg/kg bw/day in rats and 175 mg/kg bw/day in rabbits.

Metabolites

The metabolite AMPA was investigated for acute and subchronic effects, mutagenicity and teratogenicity. These studies have shown that AMPA has a lower toxicity than the parent compound and is devoid of a mutagenic or teratogenic potential.

Ecotoxicology

Table 6. Acute and chronic toxicity of Glyphosate to aquatic organisms

Species	Test duration/type	EC_{50}/LC_{50}	Assessment
Daphnia magna (with aeration)	48–hr EC_{50}	37 mg/L	Slightly toxic
Daphnia magna (Without aeration)	48–hr EC_{50}	24 mg/L	Slightly toxic
Daphnia magna	48-hr EC_{50}	13 mg/L	Slightly toxic
Gammarus pseudolimnaeus (Flow-through water)	48–hr EC_{50}	42 mg/L	Slightly toxic
Carp	96–hr EC_{50}	19.mg/L	Slightly toxic
Bluegill Sunfish (Static water)	96–hr LC_{50}	34.0 mg/L	Slightly toxic
Bluegill Sunfish (Flow-through water)	96–hr LC_{50}	5.8 mg/L	Moderately toxic
Rainbow trout (Static water)	96–hr LC_{50}	15-26 mg/L	Slightly toxic
Rainbow trout (Flow-through water)	96–hr LC_{50}	8.2 mg/L	Moderately toxic
Channel Catfish	96–hr LC_{50}	39 mg/L	Slightly toxic
Fathead minnow	96–hr LC_{50}	23 mg/L	Moderately toxic
Coho Salmon	96–hr LC_{50}	22mg/L	Slightly toxic
Chinook Salmon	96–hr LC_{50}	20 mg/L	Slightly toxic
Pink Salmon	96–hr LC_{50}	14-33mg/L	Slightly toxic

Table 7. Acute and chronic toxicity of Glyphosate to birds

Bird Species	Toxicity (mg a.i./kg)
Bobwhite quail acute and short term	8-day LC_{50} > 4640 mg/kg Non-toxic 14-day LD_{50} > 3851 mg/kg Non toxic
Bobwhite quail Reproduction	NOEC >1000 mg/kg diet
Mallard duck acute and short term	LC_{50} > 4640 mg/kg Non toxic
Mallard duck Reproduction	NOEC >1000 mg/kg diet
Chicken	LD_{50} >2500 mg/kg Non-toxic

Table 8. Toxicity* to bees

Exposure Route	Toxicity Response
Oral LD_{50}	> 100 µg/bee (Non-toxic)
Dermal LD_{50}	> 100 µg/bee (Non-toxic)

* determined with formulated product

On the basis of toxicity data and application rates for the active substance glyphosate, the risks for birds, mammals, aquatic organisms, bees, earthworms and micro-organisms in soil in observance of corresponding risk management measures are regarded as slight.

FORMULATIONS

Glyphosate liquid formulations (GIFAP code SL) and glyphosate water soluble granules (GIFAP code SG).
Registered and sold in most countries of the world.

METHODS OF ANALYSIS AND TESTING

- **Chemical analytical methods for active ingredient (including identity tests):**

  AOAC-CIPAC method 284/TC/(M)/3, CIPAC 1C, p.2132, and AOAC 983.10, 1990.
  AOAC-CIPAC method 284/SG/(M)/3, CIPAC H, p. 182, and AOAC Official Method 996.12, 1997.

  The principle is HPLC using an anion exchange column, UV detection at 195 nm and quantification by external standardisation.

  Identity Tests

  - AOAC-CIPAC method 284/TC/(M)/2, CIPAC 1C, p.2132, retention time.
  - AOAC-CIPAC method 284/SG/(M)/2, CIPAC H, p.182 for SG's, retention time.
  - Record the UV scan of the main peak of the chromatogram and compare with an UV scan of the calibration solution.
  - Spectrophotometric method. Reaction of glyphosate with sodium nitrite under acidic conditions to form *N*-nitroso-glyphosate. UV determination at 243 nm.
  - **-**

- **Method(s) for determination of relevant impurities in the technical material**

  Formaldehyde is determined by a reversed phase HPLC column, off-line derivatization with Hatzsch reagent and UV-VIS detection at 412 nm. This method has been validated from 10 - 300 ppm. (Monsanto Method No AQC 678-86).

  N-Nitroso-*N*-phosphonomethylglycine (NNG) is determined by strong anion exchange HPLC with UV-visible detection. Samples are dissolved in water and reacted with hydrobromic acid to form a nitrosyl cation; the nitrosyl cation reacts with *N*-(1-naphthyl)ethylenediamine and sulfanilamide to form a purple azo dye that is detected at 550 nm. Because nitrite ion will react with glyphosate to form NNG, all glassware and equipment must be rinsed with sulfamic acid. This method has been validated to 200 ppb in glyphosate technical and 100 ppb in formulated products (Monsanto method no AQC 684-86).

- Physical testing methods: See the specifications.

- **PHYSICAL PROPERTIES**

  The proposers declared that glyphosate produced and commercialised by Monsanto and Cheminova complies with the FAO specifications (2000).

The clause for specifying the pH range in the case of glyphosate isopropylamine salt concentrates (284.105/TK) and glyphosate soluble concentrates (284/SL) was introduced because, depending on the climatic conditions, the equilibrium glyphosate acid - glyphosate monoispropylamine salt - diisopropylamine salt will determine the potential crystallisation of glyphosate acid, which has lower water solubility than its salts.
The clause specifying the flowability of soluble granules was changed from 100% to 98% because it was too stringent. Such granules sometimes have the tendency to form loose aggregates, which may remain on the sieve but readily disappear during dissolution in water.

CONTAINERS AND PACKAGING

No special requirements have been reported for containers and packaging but metal containers should not be used unless lined with suitable material to resist the products if they are acidic.

EXPRESSION OF ACTIVE INGREDIENT (Sections 4.2.5 and 4.2.7 of the Manual)

The active ingredient content is expressed as glyphosate (acid) in g/kg or g/l (for liquid formulations at 20°C).

APPRAISAL

The current FAO specifications for glyphosate acid technical concentrates (FAO Specification 284/TK/S, 1991) and glyphosate soluble concentrates (FAO Specification 284/SL/S, 1991) were based on data submitted from Monsanto and were published 1992 (AGP:CP/301) with a correction 1994 (AGP:CP/311). The proposers for the revised specification are Monsanto Agricultural Company and Cheminova Agro A/S.

Glyphosate acid is a colourless crystalline solid without odour. It melts at 189.5 °C. The acid is of medium water solubility (10 g/l), the salts are highly soluble in water.
It is formulated as water soluble concentrates and water soluble granules, in both of which it is used as a salt (isopropylamine salt, ammonium salt or sodium salt).
Glyphosate is stable to hydrolysis in the range of pH 5 to pH 9 and relatively stable to photodegradation.

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on impurities present at or above 1 g/kg, from both of the companies.
Two impurities were identified (formaldehyde and *N*-nitroso-*N*-phosphonomethyl-glycine, NNG) as relevant and maximum limits are specified.
The same absolute limit of 1 mg/kg for NNG has been set for the TC, TK's and the formulations because this impurity may be formed during the synthesis of glyphosate acid, as well as during the subsequent steps of acid neutralisation (formation of the salt) and during the final steps of formulation.

During the synthesis, the presence of nitrites in the process water, or the presence of $[NO]_x$ in the air or oxygen, used in the oxidation process, are the main causes of the formation of *N*-nitrosoglyphosate (NNG).
During the step of acid to salt conversion, the presence of free nitrites in the water being used, might increase the level of *N*-nitrosoglyphosate.
Finally, the formulation or granulation steps, again might cause an increase in the NNG level due to the presence of free nitrites in the water used. Here also again, the $[NO]_x$ present in the air, e.g. hot air being used to dry the granules, might cause increase of NNG.

For formaldehyde the limit was set to 1.3 g/kg on a glyphosate acid basis, according to the rules of FAO as published in the Manual. This limit corresponds closely to the limit in the US OSHA regulations which was set on "as is" basis and not on an acid basis.

The differences in the impurity profiles of the two sources had been assessed by the German authorities and were regarded to be of no relevance with regard to toxicological or ecotoxicological properties. This assessment included all toxicological and ecotoxicological studies available to the German authorities. Taking the more detailed Monsanto impurity profile as the reference profile the Cheminova profile is equivalent to the Monsanto impurity profile according to the criteria given in the Manual.

Glyphosate is of low acute toxicity and shows no adverse effects with regard to carcinogenicity, mutagenicity, teratogenicity or reproduction toxicity.

The proposal for an ADI of 0.3 mg/kg bw for glyphosate based on long term studies in rats is in line with the value published by WHO based on the JMPR evaluation of 1986.

Glyphosate is of low risk to birds, mammals, aquatic organisms, bees, earthworms and micro-organisms in soil.

The proposers declared that glyphosate produced and commercialized by Monsanto and Cheminova comply with the FAO specifications (1999)

RECOMMENDATIONS

The draft specifications for glyphosate acid technical, glyphosate acid technical concentrates, glyphosate isopropylamine salt technical concentrates, glyphosate soluble concentrates and glyphosate water soluble granules, proposed jointly by Monsanto and Cheminova were regarded as acceptable by the Meeting. As the Cheminova impurity profile is covered by the Monsanto impurity profile is the Meeting recommended that the Monsanto profile should be the reference profile.

REFERENCES

- Manual on Development and Use of FAO Specifications for Plant Protection Products, January 1999, Rome.

- FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent. Group of Experts on Pesticide Specifications, 3rd Session. 5 - 8 October 1998, Rome.

- IPCS Environmental Health Criteria 159, WHO 1994, Geneva.

- IPCS, The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 1998-1999, WHO 1999, Geneva.

- CIPAC Handbook 1C, 1985

- CIPAC Handbook F, 1995

- CIPAC Handbook H, 1998

FAO SPECIFICATIONS AND EVALUATIONS FOR
PLANT PROTECTION PRODUCTS

GLYPHOSATE

EVALUATION REPORT 284/2001

Explanation

The data for glyphosate were evaluated in support of existing FAO specifications 284/TC, 284/TK, 284/SL, 284/SG (2000). The supporting data were provided by Syngenta to extend the scope of the existing specification to their product.

Uses

See Evaluation Report for glyphosate (2000).

Identity

ISO common name: Glyphosate

Chemical name:

IUPAC: *N*-(phosphonomethyl)-glycine

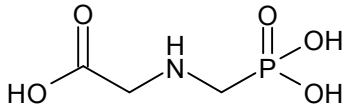
CA: *N*-(phosphonomethyl)-glycine

CAS No: 1071-83-6

CIPAC No: 284

Synonyms: none

Structural formula:



Molecular formula: $C_3H_8NO_5P$

Relative molecular mass: 169.1

Identity tests: see FAO Specification 284/TC (2000)

Physico-chemical properties of pure glyphosate

See FAO Specification 284/TC (2000)

Chemical composition and properties of glyphosate technical materials

See FAO Specification 284/TC (2000) and confidential information to this report.

Hazard summary

See Evaluation Report for glyphosate (2000).

It was recognised that the acute dermal toxicity given (< 2000 mg/kg bw) by Syngenta was higher than stated in the Evaluation Report for glyphosate (2000) (< 5000 mg/kg bw).

Justification submitted by Syngenta:

The guideline used in the acute dermal study [CTL/P/4464] was OECD 402 as specified in 91/414/EEC. In accordance with this guideline the limit dose of 2000 mg/kg was applied following a range finding test to set the dose. A limit dose at this level is, from a technical perspective, appropriate as this is approaching the maximum quantity that can be applied with reasonable confidence that the totality of the dose applied will remain in contact with the rat skin for the duration of the exposure. Applications of amounts greater than 2000 mg/kg are less likely to result in the total dose achieving and/or maintaining contact with the rat skin during the exposure period.

Hence a dermal topical application of 5000 mg/kg leading to an acute dermal MLD50 value of >5000 mg/kg does not signify a lower intrinsic acute dermal toxicity than an MLD50 of >2000 mg/kg resulting from a study using a limit dose of only 2000 mg/kg. The difference in endpoints being simply a reflection of limit dose set used in the individual studies.

It is therefore reasonable to consider that acute dermal MLD50 values in the rat of >2000 and >5000 mg glyphosate acid/kg, where the variance is only a reflection of the differing limit doses of the individual studies, indicate an equivalent profile of the acute dermal toxicity.

This justification was accepted by WHO.

Formulations

Not submitted by Syngenta

Methods of analysis and testing

Analytical method for the active ingredient (including identity tests): see FAO Specification 284/TC (2000).

Fully validated analytical methods for the impurities were provided by Syngenta.

Physical properties

See FAO Specification 284/TC (2000)

Containers and packaging

See FAO Specification 284/TC (2000)

Expression of the active ingredient

See FAO Specification 284/TC (2000)

Appraisal

The data submitted by Syngenta were in accordance with the requirements of the FAO Manual (5th edition) and supported the draft specification. The deviations from reference data set were justified by the proposer and regarded as acceptable by the evaluator.

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present at or above 1 g/kg.

The manufacturing process and the impurity profile of Syngenta were different from those submitted with the reference specification. The deviations from reference data set were >50% or 3 g/kg in the case of R025029 and R290510 impurities. However, these differences do not lead to differences in toxicological assessment, as evidenced by the data submitted by the proposer for acute oral, dermal, inhalation, skin and eye irritation and sensitization. The Syngenta product is therefore considered to be equivalent to the products upon which the reference profile is based.

Recommendations

The draft specification for technical glyphosate proposed by Syngenta was accepted by the Meeting. The proposer had requested a specification for this material as a TC but the Syngenta product is considered to be equivalent to the existing TK specification. The difference between TC acid and TK acid is the water content only and therefore the extension of the TK specification is recommended. From the production Syngenta isolates the TK acid as a wet paste with a minimum content of 760 g/kg glyphosate. This is within the reference specification for the TK.

References

See Evaluation Report for glyphosate (2000).